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TOBACCO INDUSTRY RESEARCH COMMITTEE

150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: MAY 8, 1962

1. Name of Investigator: Charles W. La Belle, Ph.D.
2. Title: Assistant Professor of Environmental Hygiene
3. Institution & Address: Jefferson Medical College
1025 Walnut Street
Philadelphia, Pennsylvania
4. Project or Subject: EFFECT OF CIGARETTE SMOKE ON PULMONARY CLEARANCE

5. Detailed Plan of Procedure:

This laboratory has in the past devoted considerable attention to the investigation of those factors which determine the rate at which inhaled particles are eliminated from the lung. Starting with an early finding that weight for weight, small uranium dioxide particles are more toxic than large (La Belle, 1947); it was successively shown that the behavior of particulates is altered by the presence of adsorbable vapors (LaBelle, Long, and Christofano, 1955); that the clearance of particulates from the lung occurs in two stages, an early rapid phase being followed by a later slow phase (LaBelle et al., 1960); that the early rapid phase involves transfer of particles to the gastrointestinal tract (Brieger and La Belle, 1959); that the early rapid phase is characterized by the appearance of large numbers of histiocytes in the lung parenchyma (La Belle and Brieger, 1959); that the correlation between pulmonary clearance and the number of free motile phagocytes (as distinct from fixed tissue histiocytes) is extremely high ($p = 0.87$) (La Belle and Brieger, 1961); that the kinetics of the appearance and disappearance of these cells corresponds to the kinetics of pulmonary clearance (La Belle and Brieger, 1960); and finally, that the release of phagocytes can be artificially stimulated by administration of carbon particles in such a way as to accelerate the elimination of previously inhaled noxious particles (La Belle et al., 1962). Studies currently in progress involve assay of the biological properties of the carbon particles (La Belle and Bevilacqua, 1962), and the establishment of a routine therapeutic procedure for emergency treatment for inhaled radioactive particles (Bevilacqua and La Belle, unpublished).

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From these findings we conclude that early-phase pulmonary clearance is the biological function of these cells, and that conversely, the rate of clearance is determined by the number of phagocytes available. There is an opposing school of thought which believes that this early clearance process is caused by and controlled by the ciliated epithelium of the bronchial tree. For example, Dalhamn and his associates at the Karolinska Institute have shown that ciliary action is depressed by ammonia and formaldehyde (Dalhamn, 1956), by sulphur dioxide (Dalhamn and Rhodin, 1956), and by cigarette smoke (Dalhamn, 1959). Although Dalhamn questions whether all the effects of smog can be related to the blocking of the cilia by sulphur dioxide (Dalhamn and Strandberg, 1961), it remains the Swedish view that blocking or even slowing of the cilia will correspondingly inhibit pulmonary clearance.

If this view is correct, it follows that the correlation between lung cancer and smoking might derive from such blocking of the defenses against inhaled carcinogens. However, we do not accept this inference as correct, and we have the techniques and apparatus available to test the question experimentally.

We have recently constructed in this laboratory an apparatus in which radioactive isotopes can be followed from organ to organ in intact rabbits. With this apparatus it is possible to determine in about a week a lung clearance curve which formerly required several months to construct by conventional methods of serial sacrifice and tissue analysis. This unit is designed to test animals in pairs, one rabbit being held as a control, the other being subjected to various trial therapies. It is proposed to use this same apparatus and technique to compare pairs of rabbits, with identical lung burdens of radioactivity, one of the pair being exposed to cigarette smoke. If the Swedish view is correct, clearance will be inhibited by the cigarette smoke; if we are correct, clearance will be unaltered or may even be slightly increased.

It has been found that about three weeks are required to accumulate enough replicate clearance curves to show practical differences between treatments with reasonable assurance; it is believed that about three months work would permit of adequate exploration of the various possibilities.

B I B L I O G R A P H Y

LaBelle, 1947: The variation of toxicity with particle-size of UO_2 dust. Federation Proceedings, 6, No. 1, March, 1947.

LaBelle, Long, and Christofano, 1955: Synergistic effects of aerosols: I. Particulates as carriers of toxic vapors. Arch. Ind. Health 11, 297-304. 1955.

LaBelle, Brieger, Goddard, Rastatter, and Zinger, 1960: Retention and effect of radioactive particulates in the lung. Am. Hyg. Jour., 21, 195-200, 1960.

Brieger and LaBelle, 1959: The fate of inhaled particulates in the early post-exposure period. Arch. Ind. Health 19, 510-515, 1959.

LaBelle and Brieger, 1959: Synergistic effects of aerosols. II. Effects on rate of clearance from the lung. Arch. Ind. Health 20, 100-105, 1959.

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LaBelle and Brieger, 1960: Basic physiologic mechanisms in the pulmonary response to inhaled particulates. Proceedings XIII International Congress on Occupational Health 1960.

LaBelle, Brieger and Vasso, 1962: Biological effects of carbon. Federation Proceedings, 21, No. 2, 1962.

LaBelle and Bevilacqua, 1962: Synergistic effects of aerosols. III. Carbon particles and air-borne ions. Amer. Ind. Hyg. Jour., (in press).

Bevilacqua and LaBelle, 1962: A proposed method for the therapeutic elimination of radioactive particles from the lung. Manuscript in preparation.

Dalhamm, 1956: Mucus flow and ciliary activity in the trachea of healthy rats and rats exposed to pulmonary irritant gas. Acta Physiologica Scand., 36 supp. 123, pp. 1-161, 1956.

Dalhamm, and Rhodin, 1956: Mucus flow and ciliary activity in the trachea of rats exposed to pulmonary irritant gas. Brit. Jour. Ind. Med., 13, 110-113, 1956.

Dalhamm, 1959: The effect of cigarette smoke on ciliary activity in the upper respiratory tract. A.M.A. Arch. Otolaryngology 70, 166-168, 1959.

Dalhamm and Strandberg, 1961: The acute effect of sulphur dioxide on the rate of ciliary beat in the trachea of the rabbit, in vivo and in vitro, with studies of the absorptional capacity of the nasal cavity. Int. Jour. Air and Water Poll., 4, 154-167, 1961.

6. <u>Budget Plan:</u>	a. Salaries	\$4,500.00
	b. Expendable Supplies	\$1,400.00
	c. Permanent Equipment	
	d. Overhead (15% of a, b, e)	915.00
	e. Other	200.00
	TOTAL	\$7,015.00

BUDGET:

Salaries:

Principal Investigator	\$2,500.00
Assistant	1,500.00
Part-time technician	500.00
TOTAL SALARIES	\$4,500.00

Expendable supplies:

Animals, isotopes, etc.	\$1,400.00
	200.00
	6,100.00
	915.00

Travel:

Overhead @ 15%

TOTAL **7,015.00**

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7. Anticipated Duration of Work: THREE MONTHS
8. Facilities and Staff Available: CHARLES W. LA BELLE - as principal investigator
D. M. BEVILACQUA - as assistant
Apparatus already built and operating.
9. Additional Requirements:
Summer salaries for principal investigator - and assistant, provision
for part-time technician, animals, isotopes and travel.
10. Additional information (including relation of work to other projects and
other sources of supply).

Grants from several sources have assisted development of techniques
to their present state. No other agency will be involved in support
of this project.

Signed CHARLES W. LA BELLE
Director of Project

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